RESPONSE IN GENERAL

On the issue of priority applicants are procedurally able to claim priority as indicated. Applicants have provided specific comments with respect to the substantive support for the claim to priority and such is clearly believed to be supported in view of these comments. Claim amendments have been made which are believed to render the 35 U.S.C. §112, second paragraph rejections moot particularly in support of the comments provided. If the Examiner continues the position with respect to the 35 U.S.C. §112, second paragraph rejections in view of the amended claims the Examiner is respectfully requested to contact the undersigned attorney at the indicated phone number to arrange for an interview to work out suitable language and thereby expedite the prosecution of this application. The 35 U.S.C. §102 and §103 rejections are believed to have been overcome in view of the claim amendments in that none of the references specifically disclose a method of delivering a polynucleotide preferentially to specific regions of the respiratory tract. The prior art merely teaches aerosolization of particles within broad ranges but does not teach applicants' invention which specifically claims forming aerosolized particles while controlling particle size so that the particles have an aerodynamic diameter range designed to travel to a specific end location within the lung. This type of specific targeting is not taught in the cited references and the combination of references provides no motivation for such a targeting method. In view of such the prior art rejections are believed to have been overcome. A more complete explanation in response to each of the rejections, if required by the Examiner, is put forth below.

Priority claim

The Office Action stated that claims 2, 6, and 7 are not supported by the specification of the parent application, now issued as U.S. Patent No. 5,906,202 ("the '202 patent"). The Office Action stated that the '202 patent specification makes no mention of targeting aerosols to the alveoli, or of the use of lipids or liposomes. The Office Action concluded that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120. Applicants respectfully traverse, and submit that all of the pending claims, including claims 2, 6, and 7, are entitled to the filing date of the '202 patent, i.e., November 21, 1996.

Elements of Priority

The present application is a conversion of the provisional application Serial No. 60/089,146 filed June 12, 1998. Thus, applicants are clearly entitled to claim priority with respect to this earlier filed provisional application in that the present application was filed on June 11, 1999 which is within one year of the filing of the original provisional application. Still further applicants point out that the present application was co-pending with application Serial No. 08/752,946 filed November 21, 1996 which application issued as U.S. Patent 5,906,202 on May 25, 1999.

The present application as well as the prior provisional application 60/089,146 and the application 08/752,946 which issued on May 25, 1999 as U.S. Patent 5,906,202 are all assigned to the same entity, i.e. assigned to Aradigm Corporation. Further, Igor Gonda is a co-inventor on all three applications. Lastly, there is co-pendency between the three applications. Thus, procedurally applicants are clearly entitled to claim priority. To the extent that this responds to the Examiner's Office Action the issue may be completely resolved. However, to the extent the Examiner intended to indicate that the claim to priority was not substantively supported within the application which eventually issued as the '202 patent, applicants have the following additional comments.

Targeting aerosols to the alveoli

The '202 patent states that the invention relates to devices and methodology for delivering aerosolized bursts of a formulation of a drug, and that "particular areas of the lung are targeted." '202 specification, column 2, lines 12-14. Areas of the lung are stated to include "alveolated region," as shown in Figures 7 and 8. '202 specification, column 8, lines 54-67; Figures 7 and 8. The '202 specification states that drugs delivered to the alveolated region generally have a systemic effect. '202 specification, column 8, lines 61-62. Thus, the '202 specification clearly contemplates targeting alveoli for delivery of compounds.

Lipids and liposomes

The '202 specification states that the genetic material may be delivered in a formulation. '202 specification, column 30, line 64, to column 31, line 3. The '202 specification states that "formulation"

describes any mixture, solution, suspension or the like which contains an active ingredient and a carrier, and that the carrier may be "any pharmaceutically acceptable flowable liquid which is compatible with the active agent." '202 specification, column 7, lines 38-40; and lines 45-47. Clearly, lipids and liposomes are encompassed by this definition. Accordingly, the '202 specification provides adequate support for lipids and liposomes.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1-20 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Claims 1-20

The Office Action stated that claims 1-20 are indefinite because they recite a relationship between the aerodynamic diameter of aerosol particles and an airway diameter of an area of the respiratory tract, but the nature of the relationship is not disclosed.

Without conceding as to the correctness of this rejection, claims 1, 17, and 20 are amended to delete the phrase "having an aerodynamic diameter related to the diameter of airways in an area of a respiratory tract."

Claims 3 and 4

The Office Action stated that claims 3 and 4 are indefinite because it is not clear exactly where the upper respiratory tract ends, and the central airways begin, and "thus one of skill in the art is not apprised of the metes and bounds of the claims." Office Action, page 3. Applicants respectfully traverse.

The specification states that "upper respiratory tract" includes the oropharyngeal region and the trachea. Specification, page 14, lines 11-14. The specification further states that the "central airways" refer to a region of the respiratory system which during normal breathing substantially removes particles larger than 3 microns in diameter. Specification, page 14, lines 15-20. This is also described in the '202 patent, which states that the upper respiratory tract includes the oropharyngeal region and the trachea, while the central airways include generations 1-16, as shown in Figure 7 of the '202 patent. Thus, one of skill in the art, from reading the specification, would know what the metes and bounds of the terms "upper respiratory tract"and "central airways." Accordingly, claims 3 and 4 as written are in compliance with the requirements of 35 U.S.C. §112, second paragraph, and need not be amended.

Claims 8 and 9

The Office Action stated that claims 8 and 9 are indefinite because they incorporate the extra step of heating the formulation, but do not disclose at what point in the method this step is to be executed. The Office Action stated that it is unclear whether the heating is performed before, or after, formation of an aerosol.

Without conceding as to the correctness of this rejection, claim 8 is amended to clarify that the heating step is performed before step (a). Support for this amendment is found in the specification on page 24, line 27 to page 25, line 7.

The Office Action further stated that claims 8 and 9 are indefinite because the meaning of the word "significant" is unclear in its context, and because it is not clear what characteristic of the particles is "adjusted." The Office Action suggested that "significant be replaced with "sufficient." Without conceding as to the correctness of this rejection, claim 8 is amended to replace "significant" with "sufficient."

Applicants submit that the rejection of claims 1-20 under 35 U.S.C. §112, second paragraph, have been adequately addressed in view of the remarks set forth above and further in view of the amendments to claims 1, 8, 17, and 20. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C. §102(e)

Claims 1-3, 5-7, and 20 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,756,353 (hereinafter "Debs"). The Examiner asserted that Debs teaches the delivery of polynucleotides to specified regions of the lungs, and, as such, anticipates 1-3, 5-7 and 20. Specifically, the Examiner noted that Debs discloses the delivery of particle sizes ranging from 0.2-2.0 μm and from 5-10 μm, respectively.

Applicants have amended independent claims 1 and 20 above. Claim 1, as amended, now recites aerosolizing a formulation comprising a polynucleotide, thereby forming aerosolized particles, while controlling a particle size of the aerosol particles to have an aerodynamic diameter range designed to travel to an end location in the airways selected from end locations consisting of the upper respiratory tract, the central airways, and the alveoli. It is respectfully submitted that Debs makes no distinction between the upper respiratory tract and the central airways, as to targeting locations. Accordingly, the particle range of

5-10 μm described by Debs would end up in both the upper respiratory and central airways locations, as described in the present specification at page 24, lines 6-9, for example. Further, the lower range identified by the Examiner does not meet the range selected for targeting the alveoli according to the present invention. In view of these distinctions, it is respectfully submitted that Debs clearly fails to anticipate claim 1 as amended.

As to claim 20, this amended claim recites determining an aerodynamic diameter range of particles comprising a polynucleotide to be delivered, based on whether a desired end location of travel is the upper respiratory tract, the central airways, or the alveoli. As noted above, Debs clearly makes no such determination or distinction. As such, it is respectfully submitted that Debs clearly fails to anticipate claim 20 as amended. As claims 2-3 and 5-7 all depend from claim 1, it is respectfully submitted that these claims are also clearly not anticipated by Debs, for at least the reasons provided above with regard to claim 1.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-3, 5-7, and 20 under 35 U.S.C. §102(e) as being anticipated by Debs, U.S. Patent No. 5,756,353, as being improper.

Claims 1, 2, 6, 7, 10, and 20 were rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent No. 5,994,314 (hereinafter "Eljamal et al."). The examiner asserted that Eljamal et al. teaches the delivery of polynucleotides to the lung where dried, powdered DNA/cationic lip complexes are aerosolized and inhaled. The Examiner further asserted that the preferred aerodynamic diameter of the complexes is 1-4 μm, which would inherently reach the alveoli.

Claim 1, as amended, now recites aerosolizing a formulation comprising a polynucleotide, thereby forming aerosolized particles, while controlling a particle size of the aerosol particles to have an aerodynamic diameter range designed to travel to an end location in the airways selected from end locations consisting of the upper respiratory tract, the central airways, and the alveoli. It is respectfully submitted that Eljamal et al. makes no distinction among the upper respiratory tract, the central airways and the alveoli, as to targeting locations. Accordingly, the particle range of 0.5 -5 μm described by Eljamal et al. would not target the upper respiratory tract, and would be specific to neither the central airways nor the alveoli. Even the preferred range of 1-4 μm would not be specific to the alveoli, as noted in the present specification at

page 23, lines 20-27, for example. In view of these distinctions, it is respectfully submitted that Eljamal et al. clearly fails to anticipate claim 1 as amended.

As to claim 20, this amended claim recites determining an aerodynamic diameter range of particles comprising a polynucleotide to be delivered, based on whether a desired end location of travel is the upper respiratory tract, the central airways, or the alveoli. As noted above, Eljamal et al. clearly makes no such determination or distinction. As such, it is respectfully submitted that Eljamal et al. clearly fails to anticipate claim 20 as amended. As claims 2, 6, 7 and 10 all depend from claim 1, it is respectfully submitted that these claims are also clearly not anticipated by Eljamal et al., for at least the reasons provided above with regard to claim 1.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 2, 6, 7, 10 and 20 under 35 U.S.C. §102(e) as being anticipated by Eljamal et al., U.S. Patent No. 5,994,314, as being improper.

Rejection under 35 U.S.C. §103

Claims 1-4, and 12-15 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Debs; U.S. Patent No. 5,497,763 (hereinafter "Lloyd et al.".and U.S. Patent No. 5,049,389 (hereinafter "Radhakrishnan"). The Examiner admitted that Debs does not disclose the select ranges for targeting the upper respiratory tract, central airways and alveoli, respectively. However, the Examiner asserted that Lloyd et al. "teaches a method for producing aerosol particles of any desired size in the range of 0.5 to 50 mm", and that Radhakrishnan teaches that aerosol droplets larger than 3 μm will reach the secondary bronchi but not the alveoli, while droplets smaller than 3 μm would target the alveoli. Given these "teachings", the Examiner concluded that it would have been obvious to use the information provided in Figure 3 of Radhakrishnan to selectively target the alveoli, central airways or upper respiratory tract with the polynucleotide containing aerosol particles of Debs. The Examiner admitted that "...the relationship between the particle diameter and lung target tissue taught by Radhakrishnan is not precisely the same as that disclosed in the instant invention..." However, the Examiner asserted that asserted that it would have been obvious to adjust the size ranges "to optimize parameters such as aerosol diameter in order to achieve targeting to a specific tissue". The Examiner further contended that one could have relied upon the

teachings of Lloyd et al. to produce particles of the appropriate size, and that one would have been motivated to do so "in order to maximize the delivery of polynucleotides to tissue *in vivo*.

Applicants respectfully traverse the Examiner's line of reasoning. Initially, Applicants note that they were unable to locate any specific disclosure by Lloyd et al. of producing particles having a size anywhere in the range of 0.5-50 mm. Contrary to the Examiner's assertion, Lloyd et al. appears to refer to a size range of 0.5-12 μm throughout the specification. Accordingly, the Examiner is respectfully requested to identify the location of the specific disclosure of 0.5-50 mm, in the next Official Action, should the Examiner continue to rely on such teaching.

With regard to the Examiner's assertion that "Radhakrishnan teaches that aerosol droplets larger than 3 μm will reach the secondary bronchi but not the alveoli" and that "Droplets smaller than 3 μm will target the alveoli", Applicants again have been unable to find such specific teachings within the reference referred to. Accordingly, the Examiner is respectfully requested to identify the location of these specific disclosures in the next Official Action, should the Examiner continue to rely on such teachings. Referring to Figure 3 of Radhakrishnan, which was also relied upon by the Examiner, this Figure appears to contradict the earlier "teachings" referred to by the Examiner. Specifically, Figure 3 appears to indicate that particles ranging from 1.1 to 2.1 μm will <u>not</u> reach the alveoli, but will target the terminal bronchi. While Applicants do not necessarily agree with the teachings of Figure 3, they do contradict the conclusions that the Examiner has apparently drawn from them. As such, it is respectfully submitted that the use of Radhakrishnan as a teaching reference is misdirected and improper.

As to the Examiner's conclusions that it would have been obvious to adjust the size ranges to optimize parameters such as aerosol diameter in order to achieve targeting to a specific tissue", the Examiner has not provided any reference or teaching which would led one of ordinary skill in the art to make such adjustments. As noted by the Examiner, Figure 3 of Radhakrishnan already purports to identify ranges of particle sizes with regard to specific locations of the airways. The Examiner has provided no other teaching reference which would have motivated one of ordinary skill in the art to modify the disclosure of Radhakrishnan. As such, there has been no *prima facie* showing of obviousness. The Examiner's further contention that one could have relied upon the teachings of Lloyd et al. to produce particles of the appropriate size, and that one would have been motivated to do so "in order to maximize the delivery of

polynucleotides to tissue *in vivo,*" appears to be specious, in that it does not appear that the references applied by the Examiner would have had such motivation as a goal, and thus there would be no impetus to veer from their teachings, absent a hindsight reliance upon the disclosure of the instant specification. Finally, as noted earlier, Lloyd et al. does not provide and suggestion or motivation for making or selecting the claimed target ranges for delivery of a polynucleotide.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-4, and 12-15 under 35 U.S.C. §103 as allegedly unpatentable over Debs in view of Lloyd et al. and Radhakrishnan, as being improper.

Claims 1, 8, 9, 11,12, and 16-19 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Lloyd et al.; Eljamal et al.; and U.S. Patent No. 5,333,106 (hereinafter "Lanpher et al."). The Examiner asserted, *inter alia*, that Eljamal et al. teaches the delivery of polynucleotides to the lung with a preferred aerodynamic diameter of the complexes including the polynucleotides to be in the range of 1-4μm, and that Lanpher et al. teaches an electronic apparatus for measuring inspiration volume and airflow, and a method for teaching patient's to inspire at a particular volume and rate. The Examiner concluded that it would have been obvious to deliver polynucleotides by the method of Lloyd et al., in order to adjust the dryness of the particle in view of ambient conditions such as humidity, and that it would further have been obvious to train patients to use the delivery method of Lloyd et al.

In view of the above amendment of independent claims 1 and 17, Applicants respectfully request reconsideration and withdrawal of this ground of rejection. Claim 1 recites, *inter alia*, controlling a particle size of the aerosol particles to have an aerodynamic diameter range designed to travel to an end location in the airways selected from end locations consisting of the upper respiratory tract, the central airways, and the alveoli. It is respectfully submitted that none of the cited references, whether taken alone or in any proper combination, discloses or teaches these features, nor would they motivate one of ordinary skill in the art to modify any of the references to do so.

Claim 17 has been amended to recite a step of calibrating a delivery device based on the inspiratory volume determined in the earlier step. Since Eljamal et al. merely discloses a training aid for practice breathing, and since there is no suggestion of calibrating a delivery device from such training exercise, it is respectfully submitted that this in no way would motivate one of ordinary skill in the art to calibrate a

device. based upon a determination of an inspiratory volume of the subject. Accordingly, it is respectfully submitted that the rejection of claim 17 is improper in view of the above amendment and remarks.

Each of claims 8, 9, 11, 12, 16, 18 and 19 depends upon one of independent claims 1 and 17. As such, it is respectfully submitted that these claims are also allowable against the cited art, for at least the same reasons provided above with regard to claims 1 and 17, respectively.

III. CONCLUSION

Applicants submit that all claims are now in condition for allowance, which action is respectfully requested. If the Examiner finds that a telephone conference would expedite prosecution, he is invited to telephone the undersigned at the number provided below.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number AERX-061.

Respectfully submitted,

Date: August 22, 2000

By: _____
Karl Bozicevic
Registration No. 28,8070

BOZICEVIC, FIELD & FRANCIS LLP
200 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

F:\DOCUMENT\AERX (Aradigm)\061\oa (05-23-00) rsp to PTO.wpd